



The Interest of phytovigilance in the prevention of adverse reactions bound to the use of Medicinal plants

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The phytovigilance is a discipline that has a main objective the monitoring of adverse effects and drug interactions consecutive to the use of herbal medicines, food supplements based on plants, and phytocosmetic and/or medicinal plants. The existence of risks of toxicity or pharmacokinetic or pharmacodynamic drug interactions between a plant and an allopathic medicinal or between related plants has required the existence of a monitoring system for this type of products; further international guidelines have defined this discipline as a legal obligation. Two phytovigilance observations were collected at the university hospital of Oran. They encourage strengthening phytovigilance strategies, sensitizing medical staff to systematically incorporate in its diagnostic approach the possibility of a toxic effect of herbal medicines or a drug interaction and drawing population attention to the danger of the irrational and excessive use of these plants.

Keywords: phytovigilance; medicinal plants

Introduction:

Herbal medicinal products are defined as plants or their drifts used to warn or treat diseases. We use the terms medicinal plant, herbalist's preparation and phytotherapeutic remedy. They are thought to be effective and well tolerated; this blind belief is wrong and dangerous because these plants contain chemical compounds as powerful as those contained in any synthetic medicine. Although the natural products are considered as pharmacological assets, they **can** be responsible for harmful or even mortal effects, and thus require a continuous and

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strict vigilance (Skalli and Soulaymani benchikh 2008, WHO 2004). The danger concerns, especially, the patients with chronic diseases, who for financial reasons or the ineffectiveness of the conventional treatment, are impelled by this type of remedy which is inexpensive and often described as the best solution, the miracle cure. Usually current treatment and traditional one coexist, which exposes the patients to side effects due to the interaction between both types of treatment (Hammiche et al. 2015). According to the Herbal Medicinal Products Committee [HMPC] of the European Medicines Agency [EMA] (Anonyme,2014) and to the department in charge of the authorization of herbal medicine within the National Agency of Safety of Medicine and health products [ANSM] (Anonyme,2014): "No specific system of Vigilance is defined regarding the risks of misuse bound to herbal products" (Lehman and Pabst 2015); the notifications concerning herbal drugs pass by the classic system of "pharmacovigilance" of the ANSM; those concerning herbal food supplements follow the directives of "Nutrivigilance", set up by the National Agency of Sanitary Safety of Food, the Environment and the Work [HANDLES]; whereas those relative to herbal medical devices and phytocosmetics are respectively a matter of the "Materiovigilance" and "Cosmetovigilance" (Anton et al., 2009), which leads to a great risk of under reporting and thus an under estimation of the side effects or interactions associated with herbal products (Lehman and Pabst 2015). It is very advisable that the clinician promote the awareness of his patients to the problem and be willing himself to signal and investigate any side effect of an unexplained source, maybe there is a herbal product behind it (Biron 1999). The aim of this work is to draw attention on the necessity of this discipline which is phytovigilance and to incite to strengthen it strategies and raise the awareness; first of the medical staff and second of the population, to the danger of the irrational and excessive use of herbal products.

The herbal medicine certainly no common place treatment

The use of plants for medicinal aim is considered as "harmless" by the public. But the reality is not always in compliance with this reputation. During the last ten years, numerous articles describing adverse reactions caused by plants were published (Prescrire, 2007). Usually, the consumption of the questioned products intends to treat benign affections, in particular: flu, weight loss or gain, insomnia, constipation, hemorrhoids, articular pain, etc. The reported adverse reactions often appeared after a prolonged treatment of several weeks, months or even more than a year, in some cases. They were highly diversified and of a different nature; several publications



dealt with liver damage (Prescrire 1996), and so, the list of hepatotoxic medicinal plants is well established (D'Arcy PF 1991). In Belgium, 70 cases of renal failure imputed to the use of Chinese plants, were signaled (Koff 1995, Pauwels and Mostapha-kara 1993). Immunoallergic reactions can be caused by a large number of plants and take different aspects such as: nettle rash and anaphylactic shock induced by the psyllium (James et al. 1991); eczema due to a tonic from the Chinese plants (Lee and Lam, 1987); etc. Other random reactions: anticholinergic syndrome (Megs et al. 1995); neuropsychiatric reactions (Jin Bu Huan 1993, Wkly Rep 1995); heartbeat disorders (OMS 1993) were also reported. A death of a newborn by hepatic veino-occlusion was published (Roulet et al. 1988), whose the mother had regularly consumed during her pregnancy a tea prepared from about ten different plants. The real cause of this incident is difficult to attribute, but it is preferable and advisable to be careful when using herbal products during pregnancy. It is necessary to set apart the still vague and ambiguous domain established by the interactions between herbal products and "classic" medicine (D'Arcy PF 1993).

The need for Phytovigilance

During these last years, we noticed an immense increase in the usage of medicinal plants all over the world; China, India and Africa in particular. The real difficulty in the supervision of these natural remedies lies in the identification of the herbal products, because the same plant or compound can have different naming, multiple constitutions and complex conformations, also it may have different compositions despite belonging to the same species, with quality deficiencies, variances in the quantities and the concentrations, the defilement and the adulterations, which are done to the collection of the various parts of the plant, in various regions, during various seasons. Add to that, the absence or the inadequacy of the labeling, the lack of information for the healthcare professionals and the consumers on medicinal plants, along with the absence of legislation and Control, and the outcome is an impossible and delicate situation. Therefore it is important to establish a surveillance system dedicated only for natural products. The main objective of which is to secure the use of the latter. Phytovigilance is a medical discipline that concerns the supervision of plants, parts of plants fresh or dried out and their extracts, when used for therapeutic purposes. So phytovigilance is the surveillance of adverse reactions



caused by pharmaceutical products with herbal origins (Prescrire 2007). The development of this discipline allowed highlighting side effects of some plants or preparations of plants, until then unsuspected, as well as numerous interactions between herbal products and other classic allopathic drugs (Ulbricht et al. 2008).

Materials and methods:

It is a study of two clinical cases of hospital patients who consumed medicinal plants which were the reason of occurrence of adverse effects to be described later.

The number of notifications received at the phytovigilance unit of the university hospital 1st November of Oran (EHUO) is certainly low, but it marks the beginning of a new very important step in securing patient care.

Results and discussion

Results

Clinical Case n°1

It is a Patient F.A, male of 49 years, hospitalized at the nephrology unit for kidney transplantation. He was on : IDEOS[®] “calcium D3”, TARDYFERRON[®] “iron Sulfate”, ZANITRA[®] “B9 vitamin”, LASILIX[®] “furosemide”, LOXEN[®] “nicardipine”, CIPROLON[®] “ciprofloxacin” and ERYTHROPOIETIN[®]. On the eve of the surgical intervention, suffering from a dry and irritating cough; the patient took a mixture of honey and medicinal plants bought on the market. Thereafter, he showed hyper leukocytosis with no particular source of infection confirmed by a peripheral blood smear. The clinician confirmed that the patient’s haematological status was correct before taking the herb tea. Accordingly, we proceeded to the botanical identification of the constituents of the herb tea and the honey, so we were able to isolate the following plants, classified by order of precedence: *Lavandula angustifolia* Mill, *Rosmarinus officinalis* L, *Origanum vulgare* L, *Glycyrrhiza glabra* L, *Juglans regia* L, *Salvia officinalis* L, *Berberis vulgaris* L, *Mentha spicata* L, *Mentha pulegium* L and *Eucalyptus* sp Labill. (Table 1)

Clinical Case n°2



Patient X; a woman of 20-years-old diagnosed with type I diabetes a year ago, admitted at the internal medicine unit of the university hospital center of Oran on the 27th of September 2015, due to a deterioration of her general status with ketoacidosis, tachycardia of over 150 beat per minute, hepatic cytolysis (Transaminases 20 N, low TP) and a kidney damage (renal failure with a creatinine clearance of 30 mL/min). The patient was dialyzed on 01st of October, the creatinine clearance normalized on the 05th of the same month (cl=90 mL/min). After further investigations; we found that during the last 3 months, the patient had stopped taking her antidiabetic treatment; "insulin" and substituted it by a natural compound prepared from medicinal plants, in the form of tea bags. She took three bags a day for the whole three months, while the posology mentioned on the labeling of the product is of one bag a day. The clinicians suspected the hepatic cytolysis to be caused by the consumption of the mixture of plants. We were aware of this case by a notification that reached us on the 10th of October 2015. We identified the botanical composition of the mixture of plants as: *Matricaria recutita* L; *Trigonella foenum graecum* L; *Salvia officinalis* L; *Nigella sativa* L, *Olea europaea* L; , *Cinnamomum cassia* Blume; , *Aloe barbadensis* Burm . (Table 1)

Discussion

Clinical Case n°1

The analysis of drug interactions showed that calcium decreases the absorption of iron salts. However analysis of the interaction between the drugs and the plants revealed the following: *Glycyrrhiza glabra* L increases the effects of certain drugs as digitalis, steroids and some diuretics; it would also increase the absorption of iron salts at the intestinal level (Williamson , 2009); *Mentha viridis* L decreases the absorption of the 85 % of iron salts by complexing it with polyphenols (Williamson , 2009); *Lavandula officinalis* L is incompatible with iron salt and iodine; it becomes toxic if combined with either (Williamson , 2009). In the absence of a clinical explanation; we concluded that it was an allergic reaction (hyperleukocytosis) caused by the consumption of the mixture of honey and plants. It is important to signal that bee products contain allergenic proteins responsible of *Contact Dermatitis* (Takahashi 1983), and for severe anaphylactic reactions, among which two deaths reported in Australia (Drew 1997), the first declared death was a young asthmatic of 11 years after his third exposition to bee products (Bullock 1994).



Species of the lamiaceae's family such as oregano; lavender; sage; mint and basil can also induce allergic reactions (Couteaux 2009). Adverse reactions are also attributable to the poor quality of herbal products, the most common causes are adulteration of herbal products with undeclared potent pharmaceutical substances, substitution or misidentification with toxic plant species (Kosalec,2009). It is most important to determine whether a reaction is caused by the way a herbal medicine has been used or prepared. Particular attention to these factors should be given when an adverse reaction is suspected in connection with the use of herbal medicines usually employed in a traditional medicine. Misdiagnosis and use outside an established tradition by poorly trained providers and practitioners can be unsafe and may lead to overdose and adverse reactions. A change in the mode of preparation may lead to entirely preventable and sometimes serious adverse reactions. (WHO, 2004)

Clinical Case n°2

According to our bibliographical research, none of these plants is listed as a hepatotoxic plant. The later does contain pyrrolizidine alkaloids (the liver poisoning evokes a sudden abdominal pain, ascites and hepatomegaly with an increase of transaminases), so toxicity is caused by the biotransformation of the unsaturated alkaloids to toxic unstable ones probably pyrrole derivatives by the cytochrome P450, but no plant mentioned earlier contains alkaloids. With these findings, we reached out to the clinicians for further inquiry, and asked for a key complementary test which was the glycated hemoglobin HbA1_C, the doctor informed us that HbA1_C was 14.6 % and that the clinical status of the patient stabilized for a few days then deteriorated on the 12th of October with Transaminases 40 N, a microcytic anemia of inflammatory origin and an icterus. Facing such a clinic, a serology was necessary; the results proved an active hepatitis B. This case although does not incriminate the consumption of plants in the occurrence of the hepatitis but it raws our attention to the necessity of raising the awareness of the population to the risks of substituting conventional treatment with traditional therapies not meant to handle heavy pathologies. Being natural products, patients wrongly believe they are always safe, others fear that healthcare professionals may have negative attitudes towards their use and do not report using such remedies to avoid confrontations. In addition,



healthcare professionals are often not likely to ask patients about their self-medication. Negative effects can result from this lack of communication, which could include adverse effects or drug-herb interactions. Patients may also substitute herbal remedies for more conventional therapies without informing their doctor. (Staines Spiteri, 2011). The risk of unexpected effects may be influenced by a user's age, gender, genetics, nutrition status, and concurrent disease states and treatments. In clinical practice recognizing adverse effects of herbal medicine is not routine and their reporting is even less frequent (Staines Spiteri, 2011). People would need to be aware that plants contain a number of bioactive compounds which cause adverse effects and toxicity to humans. Small doses of highly toxic plants are sufficient to induce severe symptoms (Vončina, 2014). We conclude that the strengthening of the phytovigilance system is crucial and justified all the more that herbal medicinal products are often used on self-medication and rarely mentioned to the doctors.

Conclusions:

Herbal medicinal products are active substances that can also be responsible for side effects, present some toxicity, and interact with other drugs "herbal or conventional". It is the reason why they were included in the reference data base of the European Union and published in the "Periodic Safety Update Reports" (Lehmann 2015). This data base contains not less than 3155 active substances; herbal drugs, preparations of medicinal plants and homeopathic medicine included. Herbal medicines do not need to be avoided, the only fundamental issue is that they should be considered as medicine and the adverse effects and potential interactions considered. Thus pharmacists and doctors should be better informed to minimize patient harm. Still it is important to specify that the phytovigilance doesn't deal only with herbal medicine, but also with medicinal plants, herbal food supplements, herbal medical devices and phytocosmetics, from which rises the necessity to develop the various secondary and related branches of this new discipline. Medicinal plants are incorporated and used in tons of products of which the requirements regarding the quality and the labeling are very disparate. Thus it is critical to gather and compare the various data, listed by the various actors of the multiple systems of the sanitary vigilance, at both the national and the international levels.

Table 1. Specifications about reported plants

Scientific name	Vernacular name	Common English name	Therapeutic and traditional medicinal properties
<i>Aloe barbadensis</i> Burm. (Asphodelaceae)	ouesbour ; mor ouesbour ; sabr, siber, sabbâra (Bellakhdar, 2006)	Aloe (Wichtl & Anton, 2003)	Powerful laxative colon, because of anthracene derivatives. The mucilaginous juice of the leaves is used in cosmetics for its anti erythematous and absorbent properties. The freshly prepared Aloe vera gel has hypoglycemic and lipid-lowering properties (Wichtl & Anton, 2003).
<i>Berberis vulgaris</i> L (Berberidaceae)	ârghîs, barbâris, âmbarbâris (Bellakhdar, 2006)	Barberry (Meliani et al., 2011)	Barberry has appetizing, stimulating digestive functions and antipyretic properties. it produces an increase of the tone and contraction of the bladder, uterus and spleen (Bellakhdar, 2006), its use during pregnancy is not recommended because it is toxic in high doses (Iserin and col, 2007).
<i>Cinnamomum cassia</i> Blume (Lauraceae)	qarfa (Bellakhdar, 2006)	Cinnamom bark (Wichtl & Anton, 2003)	It is indicated in the treatment of poor appetite, digestive problems (indigestion, dyspepsia, ulcers), of asthenia and promote weight gain. It is also used to treat urinary infections (cystitis), intestinal (dysentery, infectious diarrhea) and oral (dental pyorrhea). Also we reported aphrodisiac properties of cinnamon. (Bellakhdar, 2006)
<i>Eucalyptus</i> sp Labill. (Myrtaceae)	Kalitûs, calibtous, kritûs, ,moql (Ait Youssef, 2006)	Eucalyptus	The leaves are used as a tonic remedy, astringent, febrifuge, against respiratory infections and asthma. (Ait Youssef, 2006)
<i>Glycyrrhiza glabra</i> L, (Fabaceae)	Ärq'-sûs. (Benkhniq et al. ;2011)	Licorice	Prescribed against gastric ulcer, antispasmodic, expectorant and antitussive (Bezanger, 1980), Rhizomes are used for cleaning teeth. A



			rhizome decoction is indicated against gingivitis. (Benkhnigue et al. ;2011)
<i>Juglans regia L</i> , (<i>Juglandaceae</i>)	Djouz;l-djouz,djouza,zouz (Ait Youssef ,2006)	Walnut	The leaves are used as an astringent, antiscrofulous, depurative and antidiabetic (Ait Youssef ,2006)
<i>Lavandula angustifolia</i> Mill (<i>Lamiaceae</i>)	Khuzâma ;khzâma (Ait Youssef ,2006)	Lavender	Lavender is sedative of central nervous system , antispasmodic, hypotensive, choleric and diuretic (Bezanger,1980)
<i>Matricaria recutita L</i> (<i>Asteraceae</i>)	Babounje. (Benkhnigue et al. ;2011)	Chamomile Pin heads (Wichtl &Anton , 2003)	Mainly anti-inflammatory, antispasmodic, carminative and stomachic. The infusion is used as a sleeping aid and mild sedative (Wichtl &Anton , 2003)
<i>Mentha pulegium L</i> (<i>Lamiaceae</i>)	Feliou,Afilgou (Beloued, 2009),fliyou ;feliyu (Ait Youssef ,2006)	Pennyroyal mint	It is digestive, carminative, cholagogue, expectorant and antitussive; externally it is applied as a compress on contusions, swellings and breast bottleneck. (Beloued, 2009)
<i>Mentha spicata L</i> (<i>Lamiaceae</i>)	Na'na,nana;hana;neman;li qâma (Ait Youssef ,2006)	Spearmint	Flavoring, condiment, carminative, tonic, aphrodisiac, associated to thyme, it is used as an abortifacient .in external use, spearmint is deemed dental analgesic (Ait Youssef ,2006).
<i>Nigella sativa L</i> (<i>Renonculaceae</i>)	sanûj,habbet sawda,kammun aswad (Bellakhdar, 2006)	Black caraway (Wichtl &Anton 2003)	Nigella seeds are used as an appetizer and as a general stimulant in asthenia, tradition recognizes their deworming properties (Bellakhdar, 2006) Nigella is used as emmenagogue and galactagogue, anti tumor properties of α Hederine isolated from the seed have been demonstrated (Wichtl &Anton , 2003)
<i>Olea europaea L</i>	zaytûn,zitoun,zebûj	Olive tree	The leaves are used in internal use as hypotensive



(Oleaceae)	(Ait Youssef ,2006)		and febrifuge; externally they fall within the composition of ointments and salves as Antihaemorrhoidals (Ait Youssef ,2006)
<i>Origanum vulgare</i> L (Lamiaceae)	Zatar;zaâteur;sâter (Ait Youssef ,2006)	Oregano	Tonic, exciting, antispasmodic, anticatarrhal, treatment of diseases of the sphere rhino larynx sphere and respiratory (Ait Youssef ,2006)
<i>Rosmarinus officinalis</i> L (Lamiaceae)	Kill,hatssa louban,hassalban,azir,lazir (Beloued, 2009)	Rosemary	Antispasmodic, diuretic, stimulant, cholagogue And worming. externally cooked leaves are applied on the joint swelling and sprains (Beloued, 2009)
<i>Salvia officinalis</i> L (Lamiaceae)	sâlma,sâlmiya,swâken- nabi,bû-chûcha (Bellakhdar, 2006)	Sage	This species has cholaretic, emmenagogue, antispasmodic, antiseptic, antioxidant, astringent and antiperspirant properties. It exerts more anti lactation activity due to the presence of estrogenic substances (Bellakhdar, 2006)
<i>Trigonella foenum graecum</i> L (Fabaceae)	helba,holba,l-helba (Ait Youssef ,2006)	Fenugreek	Fenugreek because of its richness in protein and carbohydrates, has a high nutritional value and has restorative properties, by its phosphorus intake, is a neuromuscular stimulant, more hypotensive activity, cholesterol-lowering, lipid-lowering, blood-forming and galactogenic were highlighted.Trigonelline gives it pro vitamin PP properties, galactomannans emollient and anti-inflammatory (Bellakhdar, 2006)

Competing interests

The authors declare that they have no competing interests.

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